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(54) **3-AMINO-PYRIDINE DERIVATIVES FOR THE TREATMENT OF METABOLIC DISORDERS**

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(58) **Field of Classification Search** None
See application file for complete search history.

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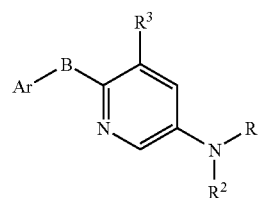
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(57) **ABSTRACT**

The present invention provides novel compounds represented by the general formula (I):



Formula (I)

their pharmaceutically acceptable salts and their pharmaceutically acceptable solvates thereof, which are useful in treating metabolic disorders related to insulin resistance or hyperglycemia. The invention also relates to a process for the manufacture of compounds of formula (I) and pharmaceutical compositions containing them.

13 Claims, No Drawings

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3-AMINO-PYRIDINE DERIVATIVES FOR THE TREATMENT OF METABOLIC DISORDERS

CROSS-REFERENCE TO RELATED APPLICATION

This application is related to our copending PCT application (PCT/IB2007/053817) entitled: METHOD FOR IDENTIFYING COMPOUNDS THAT ACT AS INSULIN-SENSITIZERS filed on the same date as the present application (20 Sep. 2007).

FIELD OF THE INVENTION

The present invention relates to compounds that are useful in treating metabolic disorders related to insulin resistance or hyperglycemia.

BACKGROUND OF THE INVENTION

Excessive weight, and in extreme cases obesity, is a widespread medical problem. This may be due in part to sedentary life styles and poor diet (high in fats and carbohydrates), as well as to a genetic predisposition in many cases. Obesity is a well-known risk factor for hypertension, Type 2 diabetes and cardiovascular diseases.

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with Type 2 diabetes mellitus are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus. There are two generally recognized forms of diabetes. In Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone that regulates glucose utilization. In Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance. Both obesity and Type 2 diabetes are characterized by peripheral tissue insulin resistance.

The prevalence of insulin resistance in glucose intolerant subjects has long been recognized. Reaven et al (American Journal of Medicine, 60, 80, 1976) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance existed in a diverse group of nonobese, nonketotic subjects. These subjects ranged from borderline glucose tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (Type 1) and noninsulin dependent (Type 2) subjects.

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Coincident with sustained insulin resistance is the more easily determined hyperinsulinemia, which can be measured by accurate determination of circulating plasma insulin concentration in the plasma of subjects. Hyperinsulinemia can be present as a result of insulin resistance, such as is in obese and/or diabetic (Type 2) subjects and/or glucose intolerant subjects, or in Type 1 subjects, as a consequence of overdose of injected insulin compared with normal physiological release of the hormone by the endocrine pancreas.

The independent risk factors such as obesity and hypertension for atherosclerotic diseases are also associated with insulin resistance. Using a combination of insulin/glucose clamps, tracer glucose infusion and indirect calorimetry, it has been demonstrated that the insulin resistance of essential hypertension is located in peripheral tissues (principally muscle) and correlates directly with the severity of hypertension (Diabetes Care, 14, 173, 1991). In hypertension of the obese, insulin resistance generates hyperinsulinemia, which is recruited as a mechanism to limit further weight gain via thermogenesis, but insulin also increases renal sodium reabsorption and stimulates the sympathetic nervous system in kidneys, heart, and vasculature, creating hypertension.

It is now appreciated that insulin resistance is usually the result of a defect in the insulin receptor signaling system, at a site post binding of insulin to the receptor. Accumulated scientific evidence demonstrating insulin resistance in the major tissues which respond to insulin (muscle, liver, adipose), strongly suggests that a defect in insulin signal transduction resides at an early step in this cascade, specifically at the insulin receptor kinase activity, which appears to be diminished (Diabetologia, 34, 848, 1991).

In the recent past, a new class of drugs, which act by reducing peripheral insulin resistance has been developed. These drugs are ligands for the nuclear receptor, peroxisome proliferator-activated receptor gamma isoform (PPAR gamma), expressed primarily in the adipose tissue. These drugs act as insulin sensitizers in reducing blood sugar and hyperinsulinemia. The most common side effects of these PPAR gamma activators are weight gain, edema, increased risk of stroke and heart attack.

Diabetic patients are at an increased risk of developing cardiovascular disease events due to risk factors such as dyslipidemia, obesity, hypertension, glucose intolerance. The presence of the above risk factors in an individual is collectively called metabolic syndrome. According to National Cholesterol Expert Panel's ATP III criteria, dyslipidemia is defined as a state in which an individual exhibits a combination of triglyceride levels of 150 mg/dl and above and HDL cholesterol level of less than 40 mg/dl in men and less than 50 mg/dl in women. (J. Am. Med. Association, 285, 2486-2497, 2001).

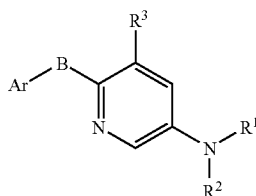
U.S. Pat. No. 6,583,157 discloses quinolinyl and benzothiazolyl compounds as PPAR modulators. U.S. Pat. No. 6,403,607 discloses sulfonamide derivatives exhibiting effects in the treatment of peptic ulcer and a drug comprising the derivative as an active ingredient.

U.S. Pat. No. 6,262,112 and U.S. Pat. No. 6,573,278 disclose aryl sulfonamides and analogues and their use in the treatment of neurodegenerative diseases.

There is a need for improved and alternative medicaments for the treatment of metabolic disorders related to insulin resistance or hyperglycemia.

SUMMARY OF THE INVENTION

The present invention provides compounds represented by the general formula (I):



Formula (I)

wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is —O—, —S—, or —NH—;

R¹ is hydrogen or S(O)₂R⁴;

R² is S(O)₂R⁴, C(O)OR⁵, or C(O)(CH₂)_n—C(O)OR⁶;

R³ is halogen, cyano, C(O)OR⁷ or C(O)NR⁸R⁹;

R⁴ is aryl;

R⁵ is (C₁-C₆)alkyl or aryl;

R⁶ is hydrogen, (C₁-C₄)alkyl, or aryl;

R⁷ is hydrogen or (C₁-C₄)alkyl;

R⁸ and R⁹ are independently hydrogen or (C₁-C₆)alkyl;

n is an integer from 1-3; and

their pharmaceutically acceptable salts and solvates.

The present invention also relates to a process for the preparation of the compounds of formula (I) their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

The present invention relates to compounds of general formula (I) that are useful in treating metabolic disorders related to insulin resistance or hyperglycemia, methods employing such compounds, and use of such compounds.

According to another aspect of the present invention, there are provided methods for manufacture of medicaments including compounds of general formula (I), which are useful for the treatment of metabolic disorders related to insulin resistance or hyperglycemia.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Listed below are definitions, which apply to the terms as they are used throughout the specification and the appended claims (unless they are otherwise limited in specific instances), either individually or as part of a larger group.

The term “alkyl,” means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or poly-unsaturated, having from one to eight carbon atoms. Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the like.

Unless stated otherwise, alkyl groups can be unsubstituted or substituted by one or more identical or different substituents. Any kind of substituent present in substituted alkyl

residues can be present in any desired position provided that the substitution does not lead to an unstable molecule. A substituted alkyl refers to an alkyl residue in which one or more, for example, 1, 2, 3, 4 or 5 hydrogen atoms are replaced with substituents, for example alkyl, halogen, hydroxyl, acyl, carboxyl, alkoxy, ester, amino, amido, acetamido, fluoroalkyl, aralkyl, acyloxy, aryl, heteroaryl, heterocyclyl, and the like.

As used herein, the term “alkoxy” or “alkoxy” refers to an alkyl group having an oxygen radical attached thereto, wherein alkyl is as defined above. The terms include, therefore, alkoxy or alkoxy groups which are substituted by one or more identical or different groups. Representative alkoxy groups include methoxy, trifluoromethoxy, ethoxy, propoxy, tert-butoxy group.

As used herein, the term “acyl” refers to any group or organic radical such as alkyl (which can be further substituted with an alkyl, alkoxy, cycloalkylamino, hydroxy or halo) attached to a carbonyl group, wherein alkyl is as defined above.

The term “heteroatom” refers to nitrogen, oxygen and sulfur. It should be noted that any heteroatom with unsatisfied valences is assumed to have a hydrogen atom to satisfy the valences.

As used herein, the term “aryl” refers to a monocyclic or bicyclic aromatic ring having up to 10 ring carbon atoms. Examples of aryl include phenyl, naphthyl, biphenyl and the like. Unless stated otherwise, aryl residues, for example phenyl or naphthyl, can be unsubstituted or optionally substituted by one or more substituents, for example, up to five identical or different substituents selected from the group consisting of halogen, alkyl, fluoroalkyl, hydroxyl, alkoxy, trifluoromethoxy, cyano, amide, CH₃CONH—, acyl, carboxyl, —COOH, sulfonyl, aryl, heteroaryl and a heterocyclyl group. Aryl residues can be bonded via any desired position, and in substituted aryl residues, the substituents can be located in any desired position. For example, in monosubstituted phenyl residues the substituent can be located in the 2-position, the 3-position, the 4-position or the 5-position. If the phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position.

The term “heteroaryl” means, unless otherwise stated, aryl groups that contain from one to four heteroatoms selected from N, O and S. The ring heteroatoms can be present in any desired number and in any position with respect to each other provided that the resulting heteroaryl system is stable.

Non-limiting examples of heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, quinolyl, isoquinolyl, quinoxalyl, and the like.

The terms “heterocyclyl”, “heterocyclic” “heterocycle” and “heterocyclo” refer to a saturated, or partially unsaturated monocyclic or bicyclic ring system containing 3, 4, 5, 6, 7, 8, 9, 10 or 11, 12, 13 or 14 ring atoms of which 1, 2, 3 or 4 are identical or different heteroatoms selected from: nitrogen, oxygen and sulfur. The heterocyclyl group may, for example, have 1 or 2 oxygen atoms and/or 1 or 2 sulfur atoms and/or 1 to 4 nitrogen atoms in the ring. Monocyclic heterocyclyl groups include 3-membered, 4-membered, 5-membered, 6-membered and 7-membered rings. Suitable examples of such heterocyclyl groups are, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, azepanyl and the like.

Bicyclic heterocyclyl groups can include two fused rings, one of which is a 5-, 6- or 7-membered heterocyclic ring and

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the other of which is a 5-, or 6-membered carbocyclic or heterocyclic ring. Exemplary bicyclic heterocyclic groups include tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydroindolyl and the like.

Unless stated otherwise, the heteroaryl and heterocyclyl groups group can be unsubstituted or substituted with one or more (e.g., up to 5), identical or different, substituents. Examples of substituents for the ring carbon and ring nitrogen atoms are: alkyl, alkoxy, halogen, hydroxyl, hydroxyalkyl, fluoroalkyl, aryloxy, amino, cyano, amide, carboxyl, acyl, aryl, heterocyclyl and the like. The substituents can be present at one or more positions provided that a stable molecule results.

The term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like). The term "halogen" means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

The term "amino" refers to the group —NH_2 which may be optionally substituted with alkyl, acyl, cycloalkyl, aryl, or heterocyclyl wherein the terms alkyl, acyl, cycloalkyl, aryl, or heterocyclyl are as defined herein above.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, as well as results in a stable compound, which does not readily undergo transformation such as by rearrangement, cyclization, elimination, etc. The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydroiodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like. Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral form of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound can differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms and the unsol-

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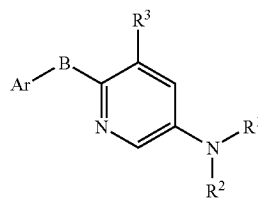
vated forms are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are within the scope of the present invention.

In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Embodiments

The present invention provides compounds represented by the general formula (I):

Formula (I)



wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is —O— , —S— , or —NH— ;

R¹ is hydrogen or $\text{S(O)}_2\text{R}^4$;

R² is $\text{S(O)}_2\text{R}^4$, C(O)OR^5 , or $\text{C(O)(CH}_2\text{)—C(O)OR}^6$;

R³ is halogen, cyano, C(O)OR^7 or $\text{C(O)NR}^8\text{R}^9$;

R⁴ is aryl;

R⁵ is $(\text{C}_1\text{—C}_6)$ alkyl or aryl;

R⁶ is hydrogen, $(\text{C}_1\text{—C}_4)$ alkyl, or aryl;

R⁷ is hydrogen or $(\text{C}_1\text{—C}_4)$ alkyl;

R⁸ and R⁹ are independently hydrogen or $(\text{C}_1\text{—C}_6)$ alkyl;

n is an integer from 1-3; and

their pharmaceutically acceptable salts and solvates.

In certain embodiments, the present invention provides compounds of formula (I) wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is —O— ;

R¹ and R² are independently H or $\text{S(O)}_2\text{R}^4$;

R³ is halogen, preferably chlorine;

R⁴ is substituted or unsubstituted phenyl; such as phenyl substituted with alkoxy, halogen, cyano, carboxylic acid, acetamido, substituted alkyl, or unsubstituted alkyl; such as: methyl or substituted-methyl substituted phenyl (e.g., 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 2-chloro-4-trifluoromethylphenyl, 3-fluoro-4-methylphenyl or 3-chloro-4-methylphenyl); mono or di-methoxy substituted phenyl (e.g., 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 4-methoxyphenyl, or 4-trifluoromethoxyphenyl);

halogen substituted phenyl, such as fluoro substituted phenyl (e.g., 4-fluorophenyl, 2,4-difluorophenyl, 2,6-dif-

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lorophenyl, 3,4-difluorophenyl 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, or 2-fluoro-4-chlorophenyl), chloro substituted phenyl (e.g., 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-trifluoromethylphenyl, 3-chloro-4-methylphenyl), or chloro and fluoro substituted phenyl (e.g., 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl); or 4-cyanophenyl; phenyl-3-carboxylic acid [phenyl-3-COOH]; or 4-acetamidophenyl [CH₃CONH-phenyl]; and

their pharmaceutically acceptable salts and solvates.

In an embodiment, the present invention provides compounds of formula (I) wherein:

Ar is isoquinolin-3-yl;

B is —O—;

R¹ is H;

R² is —S(O)₂R⁴;

R³ is halogen, preferably chlorine;

R⁴ is substituted or unsubstituted phenyl; such as phenyl substituted with alkoxy, halogen, or unsubstituted alkyl; such as:

methyl substituted phenyl (e.g., 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 3-chloro-4-methylphenyl);

mono- or di-methoxy substituted phenyl (e.g., 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 3,4-dimethoxyphenyl or, 4-trifluoro methoxyphenyl);

halogen substituted phenyl, such as fluoro substituted phenyl (e.g., 4-fluorophenyl, 2,4-difluorophenyl), chloro substituted phenyl (e.g., 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-chlorophenyl, 2-chloro-4-trifluoromethylphenyl); chloro and fluoro substituted phenyl (e.g., 2-fluoro-4-chlorophenyl); or fluoroalkyl substituted phenyl (e.g., 3-trifluoromethylphenyl, 4-trifluoromethylphenyl); or 4-cyanophenyl, phenyl 3-carboxylic acid [phenyl-3-COOH], or 4-acetamidophenyl [CH₃CONH-phenyl]; and

their pharmaceutically acceptable salts and solvates.

In an embodiment, the present invention provides compounds of formula (I) wherein:

Ar is quinolin-3-yl;

B is —O—;

R¹ is H;

R² is —S(O)₂R⁴;

R³ is halogen, preferably chlorine;

R⁴ is substituted or unsubstituted phenyl; such as phenyl substituted with alkoxy, halogen, or unsubstituted alkyl; such as:

methyl substituted phenyl (e.g., 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, or 3-fluoro-4-methylphenyl);

mono or di-methoxy substituted phenyl (e.g., 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl);

halogen substituted phenyl, such as fluoro substituted phenyl (e.g., 4-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl), chloro substituted phenyl (e.g., 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, or 2-chloro-4-trifluoromethylphenyl), or chloro and fluoro substituted phenyl (e.g., 2-fluoro-4-chlorophenyl); and

their pharmaceutically acceptable salts and solvates.

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In an embodiment, the present invention provides compounds of formula (I)

wherein:

Ar is quinolin-6-yl;

B is —O—;

R¹ is H;

R² is —S(O)₂R⁴;

R³ is halogen, preferably chlorine;

R⁴ is substituted or unsubstituted phenyl; such as phenyl substituted with alkoxy, halogen, or unsubstituted alkyl; such as:

mono or di-methoxy substituted phenyl (e.g., 3,4-dimethoxyphenyl); halogen substituted phenyl, such as fluoro substituted phenyl (e.g., 2,4-difluorophenyl), or chloro substituted phenyl (e.g., 2,4-dichlorophenyl); and

their pharmaceutically acceptable salts and solvates.

In an embodiment, the present invention provides compounds of formula (I) wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is —O—, —S—, or —NH—;

R¹ is S(O)₂R⁴;

R² is S(O)₂R⁴;

R³ is halogen;

R⁴ is substituted aryl; and

their pharmaceutically acceptable salts and solvates.

In an embodiment, the present invention provides compound of formula (I)

wherein:

Ar is quinolin-3-yl;

B is —O—;

R¹ is S(O)₂R⁴;

R² is S(O)₂R⁴;

R³ is chlorine;

R⁴ is 2,4-dichlorophenyl; and

a pharmaceutically acceptable salt and solvate.

In an embodiment, the present invention provides compounds of formula (I)

wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is —O—, —S—, or —NH—;

R¹ is H;

R² is C(O)OR⁵;

R³ is halogen;

R⁵ is (C₁-C₆)alkyl or aryl; and

their pharmaceutically acceptable salts and solvates.

In an embodiment, the present invention provides compound of formula (I), wherein:

Ar is quinolin-3-yl;

B is —O—;

R¹ is H;

R² is C(O)OR⁵;

R³ is chlorine;

R⁵ is phenyl; and

a pharmaceutically acceptable salt and solvate.

In an embodiment, the present invention provides compounds of formula (I),

wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is —O—, —S—, or —NH—;

R¹ is H;

R² is C(O)(CH₂), —C(O)OR⁶;

R³ is halogen;

R⁶ is hydrogen, (C₁-C₄)alkyl, or aryl;

n is an integer from 1-3; and

their pharmaceutically acceptable salts and solvates.

In an embodiment, the present invention provides compound of formula (I), wherein:

Ar is quinolin-3-yl;

B is —O—;

R¹ is H;

R² is C(O)(CH₂)₂—C(O)OR⁶;

R³ is chlorine;

R⁶ is hydrogen; and

a pharmaceutically acceptable salt and solvate.

Compounds of the present invention are selected from but not limited to:

2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
3-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfamoyl)benzoic acid,
3-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4,6-trimethyl benzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-cyanobenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,5-dimethylbenzenesulfonamide,
3,5-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-methylbenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-methylbenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-(trifluoromethyl)benzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzenesulfonamide,
4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-fluorobenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide,
2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide,
3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethoxy)benzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,5-dimethoxybenzenesulfonamide,
2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzene sulfonamide,
N-(4-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfamoyl)phenyl)acetamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-dimethoxybenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide,
N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide,
2,4-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide,

3,4-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide,
5 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-dimethoxybenzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethoxy)benzenesulfonamide,
2-Chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzene-sulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide,
15 4-Chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-difluorobenzenesulfonamide,
20 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,6-difluorobenzenesulfonamide,
3,5-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3-fluoro-4-methylbenzenesulfonamide,
25 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,5-dimethylbenzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4,6-trimethylbenzenesulfonamide,
30 4-chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2-fluorobenzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
2,4-Dichloro-N-(5-chloro-6-(quinolin-6-yloxy)pyridin-3-yl)benzenesulfonamide,
35 N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide,
N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide,
2,4-Dichloro-N-[(2,4-dichlorophenyl)sulfonyl]-N-[5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl]-benzenesulfonamide,
2,4-Dichloro-N-(5-chloro-6-(quinolin-6-yloxy)pyridin-3-yl)benzenesulfonamide,
45 N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide,
N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide,
Phenyl 5-chloro-6-(quinolin-3-yloxy)pyridin-3-ylcarbamate, or
4-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-ylamino)-4-oxobutanoic acid; and
their pharmaceutically acceptable salts and solvates.
Suitable compounds of the present invention are selected from but not limited to:
2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide,
60 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide,
3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide,
65 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide, or

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide, and their pharmaceutically acceptable salts and solvates.

As used herein, the terms "treat" and "therapy" and the like refer to alleviate, slow the progression, prophylaxis, attenuation or cure of existing disease (e.g., type 2 diabetes or dyslipidemia).

The term "therapeutically effective amount" as used herein is meant to describe an amount of a compound of the present invention effective in producing the desired therapeutic response in a particular patient suffering from metabolic disorders related to insulin resistance or hyperglycemia.

According to another aspect of present invention there are provided methods for manufacture of medicaments including compounds of general formula (I), which are useful for the treatment of metabolic disorders related to insulin resistance or hyperglycemia.

According to another aspect of present invention there are provided methods for the manufacture of a medicament including compounds of general formula (I), which are useful for the treatment of metabolic disorders related to insulin resistance or hyperglycemia in a mammal, which medicament is manufactured to be administered, either sequentially or simultaneously, with at least one other pharmaceutically active compound.

While it is possible that compounds of the present invention may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. Accordingly, the present invention further provides for a pharmaceutical formulation including a compound of formula (I) or a pharmaceutically acceptable salt or solvate or a prodrug thereof, for example, together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients.

The pharmaceutical composition may be in the forms normally employed, such as tablets, lozenges, capsules, powders, syrups, solutions, suspensions and the like specially formulated for oral, buccal, parenteral, transdermal, inhalation, intranasal, transmucosal, implant, or rectal administration, however oral administration is preferred. For buccal administration, the formulation may take the form of tablets or lozenges formulated in conventional manner. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycolate) or wetting agents, such as sodium lauryl sulfate. The tablets may be coated according to methods well known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives

such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides. Additionally, formulations of the present invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle (e.g., sterile, pyrogen-free water) before use.

The formulations according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (as an emulsion in an acceptable oil, for example), ion exchange resins or as sparingly soluble derivatives as a sparingly soluble salt, for example.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day or 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The formulations according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

Furthermore, in addition to at least one compound of the general formula (I), as active ingredient, the pharmaceutical compositions may also contain one or more other therapeutically active ingredients.

According to an embodiment of the present invention there is provided a method for the treatment of metabolic disorders related to insulin resistance or hyperglycemia, including administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I).

According to an embodiment of the present invention there is provided a method for the treatment of metabolic disorders related to insulin resistance or hyperglycemia, including type 2 diabetes, obesity, glucose intolerance, dyslipidemia, hyperinsulinemia, atherosclerotic disease, polycystic ovary syndrome, coronary artery disease, hypertension, aging, non alcoholic fatty liver disease, infections, cancer and stroke, including administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I). According to an embodiment of the present invention there is provided a method for the treatment of type 2 diabetes and disorders related thereto, including administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I). According to an embodiment of the present invention there is provided a method for the treatment of dyslipidemia and disorders related thereto, including administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I).

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According to an embodiment the compounds of present invention are useful for the treatment of metabolic disorders related to insulin resistance or hyperglycemia.

According to an embodiment the compounds of present invention are useful for the treatment of metabolic disorders related to insulin resistance or hyperglycemia, including type 2 diabetes, glucose intolerance, dyslipidemia, hyperinsulinemia, atherosclerotic disease, polycystic ovary syndrome, coronary artery disease, hypertension, aging, non alcoholic fatty liver disease, infections, cancer and stroke.

According to an embodiment the compounds of present invention are useful for the treatment of type 2 diabetes.

According to an embodiment the compounds of present invention are useful for the treatment of dyslipidemia.

Representative compounds useful in the treatment of metabolic disorders related to insulin resistance or hyperglycemia, in accordance with the present invention are selected from but are not limited to the following:

2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,
 3-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfa-
 moyl)benzoic acid,
 3-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-
 4-methylbenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4,6-tri-
 methyl benzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-cy-
 anobenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,5-dim-
 ethylbenzenesulfonamide,
 3,5-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-
 3-yl)benzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-meth-
 ylbenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-meth-
 ylbenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-(trif-
 luoromethyl)benzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trif-
 luoromethyl)benzenesulfonamide,
 4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)
 benzenesulfonamide,
 4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-
 2-fluorobenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-dif-
 luorobenzenesulfonamide,
 2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-
 4-fluorobenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-meth-
 ylbenzenesulfonamide,
 3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-
 3-yl)benzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trif-
 luoromethoxy)benzene-sulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,5-di-
 methoxybenzenesulfonamide,
 2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-
 4(trifluoromethyl)benzene sulfonamide,
 N-(4-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sul-
 famoyl)phenyl)acetamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,4-di-
 methoxybenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-di-
 methoxybenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-meth-
 oxybenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluo-
 robenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methoxy-
 benzenesulfonamide,

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2,4-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-
 yl)benzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methyl-
 benzenesulfonamide,
 3,4-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-
 yl)benzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-di-
 methoxybenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-di-
 methoxybenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-(trifluo-
 romethoxy)benzenesulfonamide,
 2-Chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-
 (trifluoromethyl)benzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-difluo-
 robenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-fluo-
 robenzenesulfonamide,
 4-Chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)
 benzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-difluo-
 robenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,6-difluo-
 robenzenesulfonamide,
 3,5-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-
 yl)benzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3-fluoro-4-
 methylbenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,5-dimeth-
 ylbenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4,6-trim-
 ethylbenzenesulfonamide,
 4-chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2-
 fluorobenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzene-
 sulfonamide,
 2,4-Dichloro-N-(5-chloro-6-(quinolin-6-yloxy)pyridin-3-
 yl)benzenesulfonamide,
 N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-3,4-di-
 methoxybenzenesulfonamide,
 N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-2,4-difluo-
 robenzenesulfonamide,
 Phenyl 5-chloro-6-(quinolin-3-yloxy)pyridin-3-ylcarbama-
 te,
 4-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-ylamino)-4-oxo-
 butanoic acid, and their pharmaceutically acceptable salts
 and solvates.

Suitable compounds useful in the treatment of metabolic disorders related to insulin resistance or hyperglycemia, in accordance with the present invention are selected from but are not limited to the following:

2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-
 3-yl)benzenesulfonamide,
 2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-
 4-fluorobenzenesulfonamide,
 N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-meth-
 ylbenzenesulfonamide,
 3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-
 3-yl)benzenesulfonamide,

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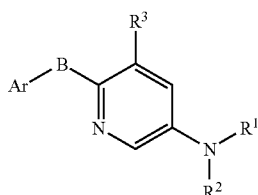
N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide,

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide, or

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide, and their pharmaceutically acceptable salts and solvates.

Preparation of the Compounds

According to a further aspect of the invention, there is provided a process for the preparation of compounds, of the general formula (I),



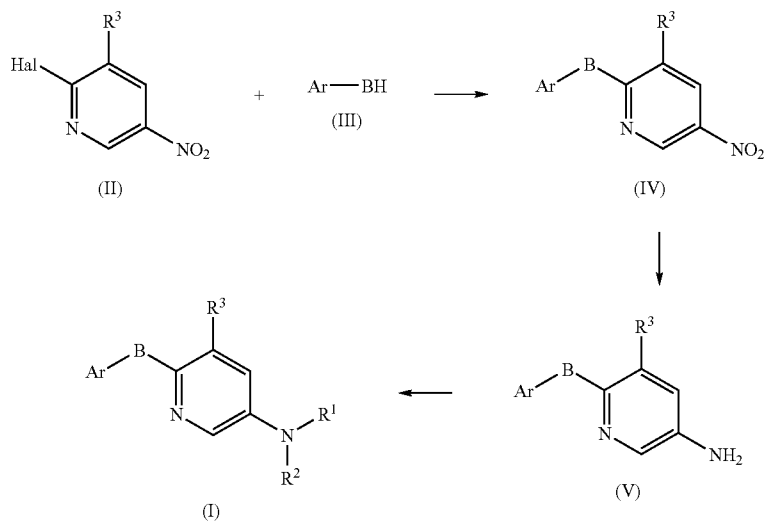
Formula (I)

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The compounds of general formula (I), according to the invention can be prepared by, or in analogy with, standard synthetic methods, and especially according to, or in analogy with, Scheme 1.

As shown in scheme 1, compounds of the present invention can be prepared by reacting compound of formula (II) wherein R^3 is as defined above and Hal is selected from fluorine, chlorine, bromine or iodine with a compound of formula (III) wherein Ar and B are as defined above, in the presence of a solvent such as dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, dioxane, or acetonitrile, optionally in the presence of a base such as cesium carbonate, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, or potassium fluoride to provide the compound of formula (IV) wherein Ar, B and R^3 are as defined above. The nitro group of compound of formula (IV) is reduced to the corresponding amino group to obtain compound of formula (V) wherein Ar, B and R^3 are as defined above. Reduction of the nitro group may be carried out by using SnCl_2 in a solvent such as ethyl acetate; or by using Fe/HCl ; or in presence of gaseous hydrogen and a catalyst such as Pd-C , Rh-C , Pt-C ; or any suitable method known in the art.

Scheme 1



wherein:

Ar is a quinoline or isoquinoline moiety which is substituted or unsubstituted;

B is $-\text{O}-$, $-\text{S}-$, or $-\text{NH}-$;

R^1 is hydrogen or $\text{S}(\text{O})_2\text{R}^4$;

R^2 is $\text{S}(\text{O})_2\text{R}^4$, $\text{C}(\text{O})\text{OR}^5$, or $\text{C}(\text{O})(\text{CH}_2)_n-\text{C}(\text{O})\text{OR}^6$;

R^3 is halogen, cyano, $\text{C}(\text{O})\text{OR}^7$, or $\text{C}(\text{O})\text{NR}^8\text{R}^9$;

R^4 is aryl;

R^5 is (C_1-C_6) alkyl or aryl;

R^6 is hydrogen, (C_1-C_4) alkyl, or aryl;

R^7 is hydrogen or (C_1-C_4) alkyl;

R^8 and R^9 are independently hydrogen or (C_1-C_6) alkyl;

n is an integer from 1-3; and

their pharmaceutically acceptable salts and solvates.

The compound of formula (V) is further converted to the desired compound of formula (I) wherein R^1 is H, R^2 is $-\text{SO}_2\text{R}^4$ and Ar, B, R^3 and R^4 are as defined above, by reacting with one equivalent of $\text{Hal-SO}_2\text{R}^4$ wherein Hal is represented by fluorine, chlorine, bromine, or iodine and R^4 is as defined above, in the presence of pyridine or triethyl amine as a base and a solvent selected from acetonitrile, dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, or dioxane.

The compound of formula (V) is converted to the desired compound of formula (I) wherein R^1 and R^2 are $-\text{SO}_2\text{R}^4$ and Ar, B, R^3 and R^4 are as defined above, by reacting with two equivalents of $\text{Hal-SO}_2\text{R}^4$ wherein Hal is represented by fluorine, chlorine, bromine, or iodine and R^4 is as defined above, at 45°C ., in the presence of triethyl amine as a base and a

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solvent selected from acetonitrile, dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, or dioxane.

The compound of formula (V) may also be converted to the desired compound of formula (I) wherein R^1 is H, R^2 is $C(O)(CH_2)_n-C(O)OH$ and Ar, B, n and R^3 are as defined above, by refluxing with an anhydride $[(CH_2)_n(CO)_2O]$, in the presence a solvent selected from benzene, toluene, tetrahydrofuran, dioxane. The acid of formula (I) may be converted to the ester wherein R^2 is $C(O)(CH_2)_n-C(O)OR^6$ and Ar, B, n, R^1 , and R^3 are as defined above and R^6 is (C_1-C_4) alkyl or aryl, by standard esterification reactions known in the literature.

The compound of formula (V) may also be converted to the desired compound of formula (I) wherein R^1 is H, R^2 is $C(O)OR^5$ and Ar, B, R^3 , and R^5 are as defined above, by refluxing with R^5 -carbonochloride, in the presence of pyridine or triethyl amine as a base and a solvent selected from acetonitrile, dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, or dioxane.

The compounds of general formula (I), wherein Ar, B, R^1 , R^2 and R^3 are as defined above may be converted into pharmaceutically acceptable salts by standard procedures known in the literature.

The compounds of this invention can be prepared as illustrated by the accompanying working examples. The following examples are set forth to illustrate the synthesis of some particular compounds of the present invention and to exemplify general processes. Accordingly, the following Examples section is in no way intended to limit the scope of the invention contemplated herein.

Experimental

List of abbreviations

HCl	Hydrochloric acid;
POCl ₃	Phosphorous oxychloride;
Cs ₂ CO ₃	Cesium carbonate
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
CPM	Counts per minute
mpk	mg per Kg.
od	Once a day
bid	Twice a day
HEPES	N-(2-hydroxyethyl)-piperazine-N'-2-ethanesulfonic acid
MP (DSC)	melting point (Differential Scanning Calorimetry)
CMC	Carboxy methyl cellulose

Preparation 1:

5-Chloro-6-(quinolin-3-yloxy)pyridin-3-amine

Step i. 2-Hydroxy-3-chloro-5-nitro pyridine

2-Hydroxy-5-nitro pyridine (1 g, 7.14 mmol) was added portion wise to 4.5 mL of concentrated HCl under constant stirring and then heated to 50° C. To this was added a solution of sodium chlorate (266 mg, 2.5 mmol) in water (4 mL). The reaction was maintained at the same temperature for an additional hour, and then cooled to 0° C. The precipitate obtained was filtered, washed with water and dried to obtain 2-hydroxy-3-chloro-5-nitro pyridine.

Yield: 850 mg (68.2%); m.p.: 195-197° C.; ¹H NMR (DMSO-d₆) δ: 8.36 (d, 1H, J=2.5 Hz), 8.65 (d, 1H, J=2.5 Hz).

Step ii. 2,3-Dichloro-5-nitro pyridine

Quinoline (0.3 mL, 2.34 mmol) was added to POCl₃ (0.5 mL 4.68 mmol) at 0° C. under nitrogen. To this stirred mixture

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was added 2-hydroxy-3-chloro-5-nitro pyridine (816 mg, 4.68 mmol) (product obtained in step i) The reaction mixture was heated at 120° C. for 2 hours, cooled to 0° C. followed by addition of ice cold water. The precipitate obtained was filtered, washed with water and dried to obtain 2,3-dichloro-5-nitro pyridine.

Yield: 630 mg (70.3%); m.p.: 53° C.; ¹H NMR (DMSO-d₆) δ: 8.94 (d, 1H, J=2.5 Hz), 9.16 (d, 1H, J=2.5 Hz).

Step iii.

3-(3-Chloro-5-nitro-pyridin-2-yloxy)-quinoline

Dry dimethylformamide (10 mL) was added to 3-hydroxy quinoline (459 mg, 3.16 mmol) under stirring. To the stirred solution was added Cs₂CO₃ (1.03 g, 3.16 mmol) at room temperature. After 30 minutes 2,3-dichloro-5-nitro pyridine (610 mg, 3.16 mmol) obtained in, step ii, was added and the stirring was continued further for 18 hours. The solvent was removed under vacuum and to the resulting mass was added water (20 mL), extracted with ethyl acetate, dried over sodium sulfate and concentrated under vacuum to obtain crude 3-(3-chloro-5-nitro-pyridin-2-yloxy)-quinoline that was purified by column chromatography (silica gel, gradient 10-30% ethyl acetate in pet ether to obtain the title compound.

Yield: 911 mg (96%); m.p.: 123-127° C.; ¹H NMR (DMSO-d₆) δ: 7.69 (t, 1H, J=6.99), 7.82 (t, 1H, J=6.89), 7.98 (d, 1H, J=8.09 Hz), 8.09 (d, 1H, J=8.39 Hz), 8.35 (d, 1H, J=2.8 Hz), 8.95 (d, 1H, 2.51 Hz), 9.03 (d, 2H, J=2.5 Hz); MS: 302 (M+1).

Step iv.

5-Chloro-6-(quinolin-3-yloxy)pyridin-3-amine

To a solution of 3-Chloro-2-quinoloxo-5-nitropyridine (2.51 g, 8.34 mmol) (obtained in step iii), in ethyl acetate (50 mL) was added stannous chloride dihydrate (7.52 g, 33.36 mmol) at room temperature. Stirring was continued further for 18 hours. Removed the solvent under vacuum and chloroform (50 mL) was added. To the stirred mixture was added 1N sodium hydroxide solution until a clear solution was obtained. Separated the organic layer and extracted with chloroform. The chloroform layer was washed with brine and water successively, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, gradient 30-50% ethyl acetate in pet ether) to obtain the title compound.

Yield: 1.85 g (81.5%); m.p.: 156-159° C.; ¹H NMR (DMSO-d₆) δ: 5.49 (s, 2H), 7.26 (d, 1H, J=2.56 Hz), 7.49 (d, 1H, J=2.57 Hz), 7.60 (td, 1H, J=8.07 and 1.19 Hz), 7.70 (td, 1H, J=6.9 and 1.46 Hz), 7.85 (d, 1H, J=2.7 Hz), 7.92 (dd, 1H, J=7.4 and 1.0 Hz), 8.01 (d, 1H, J=2.7 Hz), 8.75 (d, 1H, J=2.7 Hz); MS: 272 (M+1).

Preparation 2:

5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine

Isoquinolin-3-ol was reacted with 2,3-dichloro-5-nitro pyridine to obtain 3-(3-chloro-5-nitropyridin-2-yloxy)isoquinoline which was further converted to 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine as per the procedure described in preparation 1, step iii and iv.

¹H NMR (CDCl₃) δ: 5.49 (s, 2H), 7.21 (d, J=2.4 Hz, 1H), 7.32 (s, 1H), 7.51 (t, J=7.2 Hz, 1H), 7.55 (d, J=2.4 Hz, 1H), 7.70 (t, J=7.2 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 8.07 (d, J=8.4 Hz, 1H), 9.00 (s, 1H); MS (ES): 272 (M+1).

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Preparation 3:

5-Chloro-6-(quinolin-6-yloxy)pyridin-3-amine

Quinolin-6-ol was reacted with 2,3-dichloro-5-nitro pyridine to obtain 6-(3-chloro-5-nitropyridin-2-yloxy)quinoline which was further converted to 5-chloro-6-(quinolin-6-yloxy)pyridin-3-amine as per the procedure described in preparation 1 step iii and iv.

¹H NMR (DMSO-d₆) δ: 5.53 (s, 2H), 7.27 (brs, 1H), 7.37 (brs, 1H), 7.48-7.56 (m, 3H), 8.02 (d, 1H), 8.27 (d, 1H), 8.81 (d, 1H); MS (ES): 272.05 (M+1).

General Procedure for Preparation of Quinoline and Isoquinoline Compounds

To a stirred solution of amine (as obtained in preparation 1, 2 or 3)(1 mmol) in DCM, pyridine (1-5 mmol) was added which was followed by addition of substituted benzenesulfonylchloride (1 mmol). The reaction mixture was stirred at room temperature (25° C.). Reaction mixture was diluted using DCM, washed with water, dried over anhydrous sodium sulfate and concentrated. The crude product was purified using column chromatography (silica gel) to obtain the desired compound.

The compounds of example 1-44 and 46-48 were prepared by this procedure.

General Procedure for Salt Formation

Procedure A: Compound of formula (I) was dissolved in 1:1 ethyl acetate and DCM solvent mixture. To the clear solution 1 equivalent of corresponding acid (such as toluene sulfonic acid, methane sulfonic acid, or benzene sulfonic acid) was added and stirred for 30-45 mins at room temperature (25° C.). The salt was filtered off and characterized by ¹H NMR and MP (DSC).

Procedure B: Compound of formula (I) was dissolved in ethanol (a large excess and heating was required to obtain a clear solution). To the clear solution, 1 equivalent of the corresponding acid (such as toluene sulfonic acid, methane sulfonic acid, or benzene sulfonic acid) was added. After refluxing for 3 hours, the solvent was removed and the salt obtained was characterized by ¹H NMR and MP (DSC).

Example 1

2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per the procedure described in preparation 2) and 2,4-dichloro benzenesulfonylchloride.

m.p.: 203° C.-205° C.; ¹H NMR (DMSO-d₆) δ: 7.50-7.57 (m, 3H), 7.67-7.71 (m, 2H), 7.77 (d, 1H), 7.84-7.87 (m, 2H), 7.97 (d, 1H), 8.04 (d, 1H), 8.98 (s, 1H), 11.06 (s, 1H); MS (ES): 479.9 (M-1).

Mesylate Salt

m.p.: 211° C.-213° C.; ¹H NMR (DMSO-d₆) δ: 2.33 (s, 3H), 7.64-7.56 (m, 3H), 7.78-7.73 (m, 2H), 7.85 (d, 1H), 7.94-7.90 (m, 2H), 8.05 (d, 1H), 8.11 (d, 1H), 9.05 (s, 1H), 11.10 (s, 1H).

Sodium Salt

The compound of example 1 (250 mg, 0.522 mmol) was dissolved in excess amount (40-50 mL) of methanol and the reaction mixture was warmed at 60° C. to get a clear solution. To the stirred solution, 1.0 equivalent of sodium hydroxide was added as a solution in methanol. The solution was refluxed for 2-3 hours. After completion of the reaction, the solvent was removed and dried.

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m.p.: 291° C.-293° C.; ¹H NMR (DMSO-d₆) δ: 7.52 (s, 1H), 7.60-7.57 (dd, 2H), 7.68 (d, 1H), 7.74 (t, 1H), 7.79 (d, 1H), 7.85 (d, 1H), 7.93 (d, 1H), 8.03 (d, 1H), 8.10 (d, 1H), 9.04 (s, 1H), 11.10 (s, 1H).

Example 2

3-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfamoyl)benzoic acid

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3-(chlorosulfonyl)benzoic acid.

¹H NMR (DMSO-d₆) δ: 7.56-7.62 (m, 2H), 7.70-7.79 (m, 4H), 7.91-7.99 (m, 2H), 8.10 (d, 1H), 8.27 (d, 1H), 8.48 (s, 1H), 9.06 (s, 1H), 10.78 (s, 1H); MS (ES): 456 (M+1), 454 (M-1).

Example 3

3-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3-chloro-4-methylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.38 (s, 3H), 7.56-7.65 (m, 4H), 7.74-7.83 (m, 4H), 7.94 (d, 1H), 8.12 (d, 1H), 9.07 (s, 1H), 10.71 (s, 1H); MS (ES): 458.02 (M-1).

Example 4

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4,6-trimethyl benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2,4,6-trimethylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.24 (s, 3H), 2.50 (s, 3H), 2.54 (s, 3H), 7.05 (s, 2H), 7.56-7.62 (m, 2H), 7.68 (d, 1H), 7.74-7.79 (m, 2H), 7.94 (d, 1H), 8.12 (d, 1H), 9.06 (s, 1H), 10.77 (s, 1H); MS (ES): 454.08 (M+1).

Example 5

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-cyanobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-cyanobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.59-7.64 (m, 2H), 7.75-7.82 (m, 2H), 7.94-7.97 (m, 3H), 8.08-8.14 (m, 3H), 9.09 (s, 1H), 10.94 (s, 1H); MS (ES): 435.0 (M-1).

Example 6

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,5-dimethylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3,5-dimethylbenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 2.33 (s, 6H), 7.3 (s, 1H), 7.41 (s, 1H), 7.61 (m, 2H), 7.77 (m, 3H), 7.94 (d, 1H), 8.12 (d, 1H), 9.07 (s, 1H); MS (ES): 440.15 (M+1).

Example 7

3,5-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3,5-dichlorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.61 (m, 2H), 7.77-7.85 (m, 5H), 7.97 (m, 2H), 8.13 (d, 1H), 9.19 (s, 1H), 10.90 (s, 1H); MS (ES): 479.97 (M+1).

Example 8

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-methylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2-methylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.62 (s, 3H), 7.38 (m, 2H), 7.54-7.63 (m, 3H), 7.71 (d, 1H), 7.76 (t, 1H), 7.84 (d, 1H), 7.88-7.96 (m, 2H), 8.12 (d, 1H), 9.06 (s, 1H), 10.82 (s, 1H); MS (ES): 426.11 (M+1).

Example 9

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-methylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3-methylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.73 (s, 3H), 7.49 (d, 2H), 7.58-7.63 (m, 4H), 7.71-7.82 (m, 3H), 7.95 (d, 1H), 8.12 (d, 1H), 9.37 (s, 1H), 10.62 (s, 1H); MS (ES): 426.11 (M+1).

Example 10

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3-(trifluoromethyl)benzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.57-7.62 (m, 2H), 7.72-7.87 (m, 4H), 7.92 (d, 1H), 8.03-8.12 (m, 4H), 9.06 (s, 1H), 10.80 (s, 1H); MS (ES): 480.04 (M+1).

Example 11

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-(trifluoromethyl)benzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 7.57-7.62 (m, 2H), 7.72-7.81 (m, 3H), 7.91-7.94 (m, 1H), 7.98 (m, 4H), 8.11 (d, 1H), 9.06 (s, 1H), 10.90 (s, 1H); MS (ES): 478.0 (M-1).

Example 12

4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-chlorobenzene-1-sulfonyl chloride. ¹H NMR (DMSO-d₆) δ: 7.56-7.62 (m, 2H), 7.63-7.68 (m, 2H), 7.72-7.81 (m, 5H), 7.92 (d, 1H), 8.10 (d, 1H), 9.06 (s, 1H), 10.75 (s, 1H); MS (ES): 444.0 (M-1).

Example 13

4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-fluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-chloro-2-fluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.48 (d, 1H), 7.58-7.61 (m, 2H), 7.74-7.77 (m, 3H), 7.83-7.87 (m, 2H), 7.93 (d, 1H), 8.11 (d, 1H), 9.06 (s, 1H), 11.08 (s, 1H); MS (ES): 462.0 (M-1).

Example 14

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2,4-difluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.28 (dt, 1H), 7.54-7.63 (m, 3H), 7.73-7.79 (m, 2H), 7.85 (d, 1H), 7.89-7.97 (m, 2H), 8.12 (d, 1H), 9.07 (s, 1H), 11.03 (s, 1H); MS (ES): 448.08 (M+1).

Example 15

2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2-chloro-4-fluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.41 (dt, 1H), 7.56-7.61 (m, 2H), 7.72-7.77 (m, 3H), 7.83 (d, 1H), 7.92 (d, 1H), 8.09-8.14 (m, 2H), 9.05 (s, 1H), 11.08 (s, 1H); MS (ES): 461.95 (M-1).

Example 16

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-methylbenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 2.33 (s, 3H), 7.35 (d, 2H), 7.54-7.57 (m, 2H), 7.59-7.70 (m, 2H), 7.73-7.90 (m, 3H), 7.91 (d, 1H), 8.08 (d, 1H), 9.03 (s, 1H), 10.58 (s, 1H); MS (ES): 424.02 (M-1).

Example 17

3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3,4-dichloro-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.57-7.62 (m, 2H), 7.79-7.94 (m, 5H), 7.97 (m, 2H), 8.10 (d, 1H), 9.07 (s, 1H), 10.80 (s, 1H); MS (ES): 477.92 (M-1).

Example 18

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethoxy)benzene-sulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-(trifluoromethoxy)benzene-1-sulfonyl chloride.

¹H NMR (CDCl₃) δ: 7.25-7.32 (m, 2H), 7.47 (s, 3H), 7.54-7.62 (m, 3H), 7.72 (t, 1H), 7.80-7.85 (m, 3H), 7.85-8.03 (m, 2H), 9.10 (s, 1H); MS (ES): 493.98 (M-1).

Example 19

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,5-dimethoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2,5-dimethoxybenzene-1-sulfonyl chloride.

¹H NMR (CDCl₃) δ: 3.78 (s, 3H), 3.98 (s, 3H), 6.96 (d, 1H), 7.04-7.08 (m, 2H), 7.30 (d, 1H), 7.42 (s, 1H), 7.54 (t, 1H), 7.65-7.70 (m, 2H), 7.79-7.81 (m, 2H), 7.96 (d, 1H), 9.01 (s, 1H);

MS (ES): 472.11 (M+1).

Example 20

2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzene sulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2-chloro-4-(trifluoromethyl)benzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.57-7.62 (m, 2H), 7.73-7.78 (m, 2H), 7.86 (d, 1H), 7.96 (d, 2H), 8.12 (d, 1H), 8.16 (s, 1H), 8.25 (d, 1H), 9.05 (s, 1H), 11.28 (s, 1H); MS (ES): 511.92 (M-1).

Example 21

N-(4-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfamoyl)phenyl)acetamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-acetamidobenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 2.06 (s, 3H), 7.56-7.62 (m, 2H), 7.68-7.73 (m, 4H), 7.76-7.78 (m, 3H), 7.93 (d, 1H), 8.11 (d, 1H), 9.06 (s, 1H), 10.36 (s, 1H), 10.54 (s, 1H); MS (ES): 466.98 (M-1).

Example 22

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 3,4-dimethoxybenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 3.35 (s, 3H), 3.79 (s, 3H), 7.08 (d, 2H), 7.59-7.76 (m, 5H), 7.94 (d, 1H), 8.03 (d, 1H), 8.15 (s, 1H), 8.78 (d, 1H), 10.45 (s, 1H); MS (ES): 469.98 (M-1).

Example 23

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-dimethoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 2,4-dimethoxybenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 3.81 (s, 3H), 3.85 (s, 3H), 6.59-6.67 (m, 2H), 7.54-7.61 (m, 2H), 7.68-7.81 (m, 5H), 7.92 (d, 1H), 8.10 (d, 1H), 9.04 (s, 1H); MS (ES): 472.11 (M-1).

Example 24

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-methoxybenzene-1-sulfonyl chloride. ¹H NMR (DMSO-d₆) δ: 3.81 (s, 3H), 7.10 (d, 2H), 7.59 (m, 2H), 7.73 (m, 5H), 7.92 (d, 1H), 8.10 (d, 1H), 9.05 (s, 1H), 10.14 (s, 1H); MS (ES): 442.08 (M+1).

Example 25

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 2) and 4-fluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.43 (br s, 2H), 7.57 (br s, 2H), 7.83-7.93 (m, 5H), 8.11 (m, 2H), 9.06 (s, 1H), 10.75 (s, 1H); MS (ES): 430.08 (M+1).

Example 26

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 4-methoxybenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 3.80 (s, 3H), 7.10 (dd, 2H), 7.64 (t, 1H), 7.69 (d, 2H), 7.70 (d, 1H), 7.72-7.75 (m, 2H), 7.95 (d, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 8.78 (d, 1H), 10.44 (s, 1H); MS (ES): 440.06 (M-1).

Example 27

2,4-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 2,4-dichlorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.59-7.64 (m, 2H), 7.71-7.76 (m, 3H), 7.90-7.94 (m, 2H), 8.00 (d, 1H), 8.03 (d, 1H), 8.15 (d, 1H), 8.77 (d, 1H), 11.05 (s, 1H); MS (ES): 479.98 (M+1).

Example 28

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 4-methylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.3 (s, 3H), 7.35 (d, 2H), 7.59-7.75 (m, 6H), 7.92 (d, 1H), 8.01 (d, 1H), 8.15 (s, 1H), 8.77 (d, 1H), 10.52 (s, 1H); MS (ES): 424.09 (M-1), 426.08 (M+1).

Example 29

3,4-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 3,4-dichlorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.62 (t, 1H), 7.66 (d, 1H), 7.72-7.74 (m, 2H), 7.79 (d, 1H), 7.84 (d, 1H), 7.93-7.95 (m, 2H), 8.02 (d, 1H), 8.17 (d, 1H), 8.78 (d, 1H), 10.48 (s, 1H); MS (ES): 479.89 (M+1).

Example 30

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 3,4-dimethoxybenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 3.76 (s, 3H), 3.79 (s, 3H), 7.06 (d, 1H), 7.23 (d, 1H), 7.30 (d, 1H), 7.62 (t, 1H), 7.70-7.75 (m, 3H), 7.92 (d, 1H), 8.02 (d, 1H), 8.14 (d, 1H), 8.76 (d, 1H), 10.40 (s, 1H); MS (ES): 469.98 (M-1).

Example 31

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-dimethoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 2,4-dimethoxybenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 3.79 (s, 3H), 3.83 (s, 3H), 6.57 (d, 1H), 6.65 (s, 1H), 7.58-7.75 (m, 5H), 7.91 (d, 1H), 8.01 (d, 1H), 8.12 (s, 1H), 8.75 (d, 1H), 10.23 (s, 1H); MS (ES): 470.02 (M-1).

Example 32

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethoxy)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 4-trifluoromethoxybenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.56-7.64 (m, 3H), 7.71-7.79 (m, 2H), 7.86-7.94 (m, 3H), 8.01 (d, 1H), 8.16 (s, 1H), 8.78 (s, 1H), 9.06 (s, 1H), 10.74 (s, 1H); MS (ES): 493.99 (M-1).

Example 33

2-Chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzene-sulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 2-chloro-4-(trifluoromethyl)benzene-1-sulfonyl chloride. ¹H NMR (DMSO-d₆) δ: 7.60 (s, 1H), 7.72-7.77 (m, 3H), 7.90 (s, 2H), 8.00 (s, 1H), 8.13-8.20 (m, 3H), 8.75 (s, 1H), 11.21 (s, 1H); MS (ES): 513.99 (M+1).

Example 34

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 2,4-difluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.23-7.29 (dt, 1H), 7.52-7.64 (m, 2H), 7.70-7.78 (m, 3H), 7.86-7.94 (m, 2H), 8.01 (d, 1H), 8.16 (d, 1H), 8.77 (d, 1H), 10.99 (s, 1H); MS (ES): 445.92 (M-1).

Example 35

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 4-fluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.12 (d, 1H), 7.36 (t, 2H), 7.57-7.62 (m, 2H), 7.68-7.78 (m, 3H), 7.91 (d, 1H), 8.01 (d, 1H), 8.08 (s, 1H), 8.71 (s, 1H), 10.40 (s, 1H); MS (ES): 429.95 (M+1).

Example 36

4-Chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 4-chlorobenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 7.58-7.66 (m, 4H), 7.70-7.76 (m, 4H), 7.91 (dd, 1H), 8.01 (d, 1H), 8.15 (d, 1H), 8.77 (d, 1H), 10.97 (s, 1H); MS (ES): 446.00 (M+1).

Example 37

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,4-difluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 3,4-difluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.61-7.69 (m, 3H), 7.74-7.78 (m, 2H), 7.80 (d, 1H), 7.84 (t, 1H), 7.94 (d, 1H), 8.04 (d, 1H), 8.19 (d, 1H), 8.80 (d, 1H), 10.71 (s, 1H); MS (ES): 448.03 (M+1).

Example 38

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,6-difluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 2,6-difluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.29 (t, 2H), 7.60 (dt, 1H), 7.70-7.75 (m, 2H), 7.81 (d, 1H), 7.84 (d, 1H), 7.94 (d, 1H), 8.03 (d, 1H), 8.18 (d, 1H), 8.92 (d, 1H), 11.27 (s, 1H); MS (ES): 448.03 (M+1).

Example 39

3,5-Dichloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 3,5-dichlorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.64 (d, 1H), 7.74-7.78 (m, 3H), 7.82 (d, 1H), 7.94 (d, 2H), 8.01 (s, 1H), 8.04 (d, 1H), 8.19 (d, 1H), 8.80 (d, 1H), 10.79 (s, 1H); MS (ES): 479.94 (M+1).

Example 40

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3-fluoro-4-methylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 3-fluoro-4-methylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.28 (s, 3H), 7.48-7.54 (m, 3H), 7.64 (d, 1H), 7.72 (d, 1H), 7.75 (d, 1H), 7.78 (d, 1H), 7.94 (d, 1H), 8.04 (d, 1H), 8.18 (d, 1H), 8.79 (d, 1H), 10.65 (s, 1H); MS (ES): 444.04 (M+1).

Example 41

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-3,5-dimethylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 3,5-dimethylbenzene-1-sulfonyl chloride.

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¹H NMR (DMSO-d₆) δ: 2.31 (s, 6H), 7.29 (s, 1H), 7.39 (s, 2H), 7.61 (t, 1H), 7.71-7.78 (m, 3H), 7.94 (d, 1H), 8.04 (d, 1H), 8.17 (d, 1H), 8.79 (d, 1H), 10.51 (s, 1H); MS (ES): 440.06 (M+1).

Example 42

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2,4,6-trimethylbenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 2,4,6-trimethylbenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 2.31 (s, 3H), 2.50 (s, 6H), 7.04 (s, 2H), 7.62-7.66 (m, 3H), 7.71 (dt, 1H), 7.92 (d, 1H), 8.03 (d, 1H), 8.14 (d, 1H), 8.77 (d, 1H), 10.52 (s, 1H); MS (ES): 454.09 (M+1).

Example 43

4-chloro-N-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl)-2-fluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and 4-chloro-2-fluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.44 (dd, 1H), 7.58 (dt, 1H), 7.70-7.80 (m, 5H), 7.86 (d, 1H), 8.01 (d, 1H), 8.15 (d, 1H), 8.77 (d, 1H), 11.03 (s, 1H); MS (ES): 464 (M+1).

Example 44

N-(5-Chloro-6-(quinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) and benzenesulfonyl chloride. ¹H NMR (DMSO-d₆) δ: 7.57-7.76 (m, 9H), 7.92 (d, 1H), 8.01 (d, 1H), 8.15 (s, 1H), 8.77 (s, 1H), 10.59 (s, 1H); MS (ES): 411.99 (M+1).

Example 45

2,4-Dichloro-N-[(2,4-dichlorophenyl)sulfonyl]-N-[5-chloro-6-(quinolin-3-yloxy)pyridin-3-yl]-benzenesulfonamide

Dry dichloromethane (15 mL) was added to 5-Chloro-6-(quinolin-3-yloxy)-pyridin-3-yl amine (250 mg, 1 mmol) obtained in preparation 1. To the stirred solution was added 2,4-dichlorobenzenesulfonyl chloride (492 mg, 2.2 mmol) followed by the addition of triethylamine (2.2 mmol). The reaction mixture was then maintained at 45° C. for 15 hours, cooled to room temperature (25° C.) and diluted with dichloromethane. The dichloromethane layer was washed with water, dried over sodium sulfate and concentrated under vacuum to get the crude, which was further purified by column chromatography (silica gel).

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Yield: 483 mg (76%); NMR (CDCl₃) δ: 7.47 (dd, 2H); 7.54 (d, 2H); 7.59 (td, 1H); 7.72 (ddd, 1H); 7.84 (d, 1H); 7.86 (d, 1H); 7.90 (d, 1H); 8.00 (d, 1H); 8.14 (m, 3H); 8.82 (d, 1H).

Example 46

2,4-Dichloro-N-(5-chloro-6-(quinolin-6-yloxy)pyridin-3-yl)benzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-6-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 3) and 2,4-dichlorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 7.55-7.70 (m, 3H), 7.77-7.92 (m, 4H), 8.03-8.06 (m, 2H), 8.31 (m, 1H), 8.88 (m, 1H), 11.15 (m, 1H); MS (ES): 479.9 (M+1).

Example 47

N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-6-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 3) and 3,4-dimethoxybenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 3.78 (s, 3H), 3.80 (s, 3H), 7.07-7.17 (m, 1H), 7.34 (s, 2H), 7.83-7.96 (m, 5H), 8.31 (d, 1H), 8.83 (d, 1H), 9.15 (d, 1H), 10.70 (s, 1H); MS (ES): 472.07 (M+1)

Example 48

N-(5-Chloro-6-(quinolin-6-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide

The title compound was prepared by reacting 5-chloro-6-(quinolin-6-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 3) and 2,4-difluorobenzene-1-sulfonyl chloride.

¹H NMR (DMSO-d₆) δ: 6.97-7.17 (m, 1H), 7.27-7.55 (m, 1H), 7.66-7.74 (m, 1H), 7.86-7.99 (m, 3H), 8.08 (t, 1H), 8.36 (m, 1H), 8.63 (t, 1H), 8.88 (d, 1H), 8.94 (d, 1H), 11.20 (brs, 1H);

MS (ES): 448.04 (M+1).

Example 49

Phenyl

5-chloro-6-(quinolin-3-yloxy)pyridin-3-ylcarbamate

The title compound was obtained by reacting 5-chloro-6-(quinolin-3-yloxy)pyridin-3-amine (obtained as per procedure described in preparation 1) with phenyl carbonochloride.

¹H NMR (DMSO-d₆) δ: 10.59 (s, 1H), 8.82 (d, 1H), 8.21 (d, 1H), 8.16 (d, 2H), 8.04 (d, 1H), 7.95 (d, 1H), 7.73 (dt, 1H), 7.61 (t, 1H), 7.42 (t, 2H), 7.26 (d, 1H), 7.23 (d, 2H).

Example 50

4-(5-chloro-6-(quinolin-3-yloxy)pyridin-3-ylamino)-4-oxobutanoic acid

5-Chloro-6-(quinolin-3-yloxy)-pyridin-3-yl amine (1 mmol) (obtained as per procedure described in preparation 1) was dissolved in toluene under heating. To the clear solution

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was added succinic anhydride (1 mmol) and refluxed at 120° C. for 6 hours. The solvent the evaporated and the crude obtained was purified by column chromatography to provide the title compound.

¹H NMR: (DMSO-d₆) δ: 12.14 (brs, 1H), 10.36 (s, 1H), 8.80 (s, 1H), 8.39 (s, 1H), 8.02 (m, 4H), 7.64 (d, 2H), 2.48 (m, 4H).

Pharmacology

The efficacy of the present compounds can be determined as described below. The exemplified pharmacological assays, have been carried out with the compounds of the present invention and their pharmaceutically accepted salts.

In Vitro Model Exhibiting Insulin Resistance (IR Assay)

Example 51

The assay was designed as in the reference, British Journal of Pharmacology, 130, 351-58, 2000, the disclosure of which is incorporated by reference for the teaching of the assay. The solution of test compound (10 μM/mL) was prepared in DMSO.

Rosiglitazone (0.1 μM in DMSO) was used as standard.

Differentiation into adipocytes was induced by the known methods as described below. (See, also, J. Biol. Chem., 260, 2646-2652, 1985, the disclosure of which is incorporated by reference for the teaching of adipocyte differentiation)

Culture medium containing 0.5 nM 1-methyl-3-isobutylxanthine (IBMX), 0.25 μM dexamethasone, 5 μg/ml insulin (bovine/human), 10 mM HEPES buffer and fetal bovine serum (FBS) 10% by volume in Dulbecco's modified Eagle's medium (DMEM) was used for differentiation.

3T3 L1 fibroblasts were seeded in 24- or 6-well plates at a density of 0.5-2×10⁴ cells/well and were allowed to reach maximal confluency.

The confluent fibroblasts were exposed to culture medium for 2 days. After this period, fresh culture medium (DMEM) containing only insulin was used, 10% FBS was added and cultured for 4 days with change of medium every 2 days. After 7 days the cultures received DMEM containing 10% FBS with no exposure to insulin. By the end of 8-10 days, more than 95% of the cells have become differentiated into adipocytes.

The mature adipocytes were exposed to dexamethasone, 100 nM added in ethanol, in culture medium and incubated for 2 days. On the third day, solution of test compound was added along with 100 nM dexamethasone containing medium for 4 days with a change in medium after every 2 days. Vehicle control contained 1% v/v of DMSO. Rosiglitazone was used as a standard and was added at a concentration of 0.1 μM in DMSO, along with 100 nM dexamethasone containing medium for 4 days with a change in medium after every 2 days. After a total period of 6 days, the cells were processed for glucose uptake as follows.

The insulin resistant adipocytes were exposed to serum-free DMEM containing 0.1% bovine serum albumin for 3-4 hours at 37° C. in CO₂ atmosphere. The test compound was also present during this period. After 3-4 hours, the medium was aspirated and replaced with Krebs's Ringer phosphate (KRP) buffer at pH 7.4 and with human/porcine insulin, 200 nM. The cells were incubated for 30 minutes at 37° C. At the end of 30 minutes, 0.05 or 0.1 μCi of ¹⁴C-2-deoxyglucose was added to each well of either 24- or 6-well plates respectively and was incubated for exactly 5 minutes. After exactly 5 minutes, the plates were transferred to ice trays and medium was rapidly aspirated. The cell layer was washed twice with ice-cold phosphate buffered saline, (PBS), pH 7.4. Finally the cell layer was lysed with 150 μl of 0.1% sodium dodecyl sulfate (SDS) and the radioactivity of the cell lysate was determined in liquid scintillation counter. Non-specific glucose uptake was assayed in wells exposed to cytochalasin B,

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inhibitor of glucose transport. Compounds that showed statistically significant increase in the glucose transport/uptake expressed as CPM/well above the level in cells exposed to insulin vehicle are considered actives in this assay. The cut off limit for activity in this IR assay was defined as the increase 1.50 fold of vehicle, assay value of 1.0 for vehicle. Activity was also expressed as % of Rosiglitazone, which is used as a standard for comparison. Statistical analysis was performed using unpaired t-test.

The results are summarized in Table 1.

TABLE 1

Activity of compounds in insulin resistance model			
Sr. No.	Compound of example No.	Fold activity*	% of Rosiglitazone**
	Rosiglitazone	2.60 ± 0.1	100
01	1	2.41 ± 0.06	78.75 ± 3.55
02	3	2.30 ± 0.16	52 ± 6.5
03	5	2.41 ± 0.12	55.1 ± 4.8
04	13	1.40 ± 0.07	19.5 ± 3.51
05	15	1.70 ± 0.02	45.25 ± 1.04
06	16	1.60 ± 0.13	38.47 ± 7.98
07	17	1.26 ± 0.02	21.20 ± 1.5
08	18	1.77 ± 0.10	65
09	19	1.67 ± 0.13	50 ± 10.12
10	20	2.40 ± 0.68	36.7 ± 0.96
11	22	1.76 ± 0.58	15.8 ± 1.8
12	24	1.80 ± 0.32	46.2 ± 23.8
13	26	2.19 ± 0.09	66.48 ± 5.26
14	27	2.01 ± 0.23	57 ± 15.64
15	28	2.60 ± 0.17	71.77 ± 7.48
16	29	2.01 ± 0.09	76 ± 6.11
17	30	1.84 ± 0.02	62.51 ± 1.0 . . . 12
18	33	2.58 ± 0.11	68.59 ± 4.81
19	34	1.70 ± 0.08	43.59 ± 4.77
20	35	2.44 ± 0.08	62.36 ± 3.51
21	45	2.13 ± 0.04	59.5 ± 2.26
22	48	1.82 ± 0.13	36.7 ± 7.3

*fold activity over vehicle

**comparison with Rosiglitazone

Conclusion: Representative compounds of the present invention showed insulin sensitizing activity in increasing glucose uptake in the insulin resistance model.

Example 52

(a) Human PPAR γ Transactivation Assay

The assay was designed as in the reference, Biochem. Biophys. Res. Comm. 175:865-871, 1991, the disclosure of which is incorporated by reference for the teaching of the assay. Human PPAR γ activity was evaluated by transactivation using a luciferase reporter gene. The pBL-TK-luciferase reporter plasmid AOX-3 $\times$ PPRE-TK-LUC contains three copies of the rat acyl CoA oxidase PPRE cloned upstream of the minimal herpes simplex virus thymidine kinase (TK) promoter. Human full length PPAR γ cDNA was cloned into pSG5 expression vector (Stratagene, La Jolla, Calif.).

HEK293 cells were seeded in 24 well plates and grown in DMEM supplemented with 10% (v/v) FCS. After 24 hours, they were transfected with 100 ng of hPPAR γ receptor and 300 ng of AOX-3 $\times$ PPRE-LUC reporter construct per well using Fugen 6 transfection reagent (Roche, Indianapolis, Ind.). Test compounds or Rosiglitazone (dissolved in DMSO) were added 24 hours after transfection. The control was 0.1% DMSO. After 48 hours, transactivation activity was determined by luciferase assay using Steady Glow reagent (Promega, Madison, Wis.). The results are summarized in Table 2.

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TABLE 2

Activity of Compound 1 in human PPAR transactivation assay	
Compound of example No.	PPAR γ activity (% of rosiglitazone)
Rosiglitazone	100
1	23
26	19.3

(b) Mouse PPAR γ Assay

The assay was designed as in the reference, Blood, 104(5), 1361-8, 2004, the disclosure of which is incorporated by reference for the teaching of the assay.

3T3-L1 fibroblasts were seeded in 6-well plates at a density of 4×10^4 cells/well and cultured in DMEM containing 10% calf serum. After 4-5 days, when the cells become confluent, each of test compound was added (from a 20 mM stock in DMSO) to the final concentration of 50 μ M in DMEM supplemented with 10% FCS. Rosiglitazone was added (from 10 mM stock) to a final concentration of 10 μ M. The plates were incubated for 72 hrs at 37° C. in a CO $_2$ incubator with fresh medium containing test substances added after first 48 hrs. After 72 hrs, the medium was removed; the cell layer was washed and processed for the PPAR γ assay as per the instruction of the manufacturer (Active Motif, North America, California, USA). PPAR γ activation was determined using 96-well ELISA assay as per the instruction manual (TransAM PPAR γ , Active Motif, Cat 0.40196). Assay Readout was absorbance output from spectrophotometer for the mouse PPAR γ assay. Luminescence data output was recorded for the human PPAR γ assay.

The activity of a compound was expressed as relative activity compared to Rosiglitazone, the reference compound used as positive control. The results are summarized in Table 3.

TABLE 3

Activity of Compound 1 in Mouse PPAR assay	
Compound of example No.	PPAR γ activity (% of rosiglitazone)
Rosiglitazone	100
1	12.4
15	0
16	18.85
17	12.57
30	8.18
34	8.17

Conclusion: In the selectivity assays for human and mouse PPAR γ , the compounds of the present invention did not exhibit any PPAR γ activation.

In Vivo Biological Experiments

Note: All animal experimental procedures were approved by Animal Ethics Committee. Compounds which were found active in example 51 were subjected to in vivo evaluation in animal models of insulin resistance.

Example 53

Screening in db/db BL/6J Mice

The protocol was designed as in references.

1. Metabolism, 53(12), 1532-1537, 2004.
2. American Journal of Hypertension, 17(5), Supplement 1, S32, 2004.

The disclosures of these two references are incorporated by reference for the teaching of the protocol.

The screening of compounds was based on their ability to reduce the plasma glucose levels in genetically diabetic db/db BL/6J mice.

Male db/db mice (obtained from the Animal House of Nicholas Piramal Research Centre, Goregaon, Mumbai, India) were used for this study (body weight in the range of 30-40 g and age is 6-8 weeks) and were kept eight per cage in individually ventilated cages at controlled temperature (22±1° C.) and humidity (45±5%). Food and water were provided ad libitum during their laboratory stay, except for four hours fasting prior to blood sample collection. 12 hours light and dark cycle was followed during the whole study period.

After 4 hours fasting blood samples were collected from mice. Mice showing plasma glucose levels between 300 to 500 mg/dl were divided in groups (8-10 per group) such that the mean plasma glucose levels and variation within the group, for each group, is nearly same. After grouping, mice in respective groups received treatment with 0.5% CMC vehicle, standard compound or test compounds for 10 days. Rosiglitazone was used as a standard.

After 4 hours fasting, mice were anaesthetized using isoflurane (inhalation anesthetic), and blood samples were collected through the retro orbital plexus. Collected blood samples were centrifuged at 7000 rpm for 10 minutes at 4° C.; Separated plasma was used for estimation of plasma glucose using diagnostic kits (Diasys, Germany). Plasma glucose levels of treated groups were normalized with control group using the following formula, which accounted for the changes in control group.

Formula used for normalization was

$$*:\{1-(\text{Ratio of mean plasma glucose levels of control group on day 10 to day 0})/(\text{Ratio of plasma glucose levels of treated group on day 10 to day 0})\}\times 100.$$

The results are summarized in Table 4.

TABLE 4

Reduction in the plasma glucose levels in genetically diabetic db/db BL/6J mice					
Compounds tested in db/db mice			Rosiglitazone tested in db/db mice		
Sr. No	Compound of example No.	Dose (10 days)	Normalization with control*	Dose (10 days)	Normalization with control*
01	1	150 mpk od	43.2 ± 15.7	10 mpk od	93.8 ± 22.7
02	24	150 mpk od	Inactive	10 mpk od	55.0 ± 11.4
03	26	100 mpk bid	41.90 ± 3.84	5 mpk bid	54.52 ± 4.92
04	30	50 mpk bid	76.2 ± 19.2	5 mpk bid	107.9 ± 15.1
05	34	50 mpk bid	57.2 ± 19.1	5 mpk bid	83.6 ± 12.8

Formula used for normalization:

$$*:\{1-(\text{Ratio of mean plasma glucose levels of control group on day 10 to day 0})/(\text{Ratio of plasma glucose levels of treated group on day 10 to day 0})\}\times 100$$

Conclusion: Representative compounds of present invention showed significant glucose lowering activity in the animal model of diabetes.

Example 54

Evaluation of Lipid Levels (Dyslipidemia)

The assay was designed as in the reference, Metabolism, 49 (1), 22-31, 2000, the disclosure of which is incorporated by reference for the teaching of the assay.

Seven groups of male db/db mice (8 animals per group) were used. Animals were orally dosed twice a day (bid) for an extended period of fifteen days, with either the vehicle or compound 1 (5 mpk, 25 mpk, 50 mpk, 100 mpk and 200 mpk) or with the standard drug, Rosiglitazone (5 mpk). Body weight was measured daily. On day 15, the animals were deprived of food for 4 hours after the last dose administration. Blood was collected at the end of the 4-hour period using heparinised capillaries by a retro-orbital puncture. Plasma samples were analyzed for glucose, triglyceride, cholesterol, using the autoanalyser.

Compound of example no. 1 exhibited triglyceride-lowering ability in db/db mice at all the doses tested. The compound caused plasma triglyceride reductions ranging from 28% to 42% with the higher doses inducing higher reduction. Rosiglitazone, in the same study caused 40% decrease in plasma triglyceride levels.

Compound of example no. 1 tested at doses higher than 50 mpk, induced 26% reduction in cholesterol levels. Rosiglitazone lowered cholesterol levels by a similar extent of 27%.

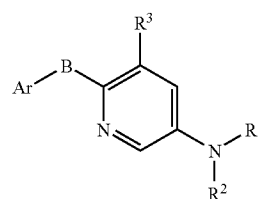
Conclusion: In db/db mice, Compound of example no. 1 was as efficacious as Rosiglitazone, in lowering lipid levels.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise. All publications and patent applications in this specification are indicative of the level of ordinary skill in the art to which this invention pertains.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

We claim:

1. A compound of general formula (I) or a pharmaceutically acceptable salt thereof,



Formula (I)

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wherein

Ar is an isoquinoline moiety which is substituted or unsubstituted;

B is —O—;

R¹ is hydrogen or S(O)₂R⁴;

R² is S(O)₂R⁴;

R³ is halogen, cyano, C(O)OR⁷, or C(O)NR⁸R⁹;

R⁴ is substituted or unsubstituted aryl;

R⁷ is hydrogen or (C₁-C₄)alkyl; and

R⁸ and R⁹ are independently hydrogen or (C₁-C₆)alkyl.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

Ar is an isoquinoline moiety which is substituted or unsubstituted;

B is —O—

R¹ is H;

R² is S(O)₂R⁴;

R³ is chlorine; and

R⁴ is phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 2-chloro-4-trifluoromethylphenyl, 3-fluoro-4-methylphenyl, 3-chloro-4-methylphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-fluoro-4-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-chloro-4-trifluoromethylphenyl, 3-chloro-4-methylphenyl, 2-chloro-4-fluorophenyl, 4-cyanophenyl, phenyl-3-carboxylic acid [phenyl-3-COOH], or 4-acetamidophenyl [CH₃CONH-phenyl].

3. A compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein

Ar is isoquinolin-3-yl;

B is —O—;

R¹ is H;

R² is —S(O)₂R⁴;

R³ is chlorine; and

R⁴ is 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 3-chloro-4-methylphenyl, 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 3,4-dimethoxyphenyl, 4-trifluoromethoxyphenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-chlorophenyl, 2-chloro-4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-fluoro-4-chlorophenyl, 4-cyanophenyl, phenyl-3-carboxylic acid [phenyl-3-COOH] or 4-acetamidophenyl [CH₃CONH-phenyl].

4. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

Ar is an isoquinoline moiety which is substituted or unsubstituted;

B is —O—;

R¹ is S(O)₂R⁴;

R² is S(O)₂R⁴;

R³ is halogen; and

R⁴ is substituted aryl.

5. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,

3-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfamoyl)benzoic acid,

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3-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4,6-trimethyl benzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-cyanobenzenesulfonamide,

3,5-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-methylbenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-methylbenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3-(trifluoromethyl)benzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzenesulfonamide,

4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,

4-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2-fluorobenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-difluorobenzenesulfonamide,

2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide,

3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethoxy)benzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,5-dimethoxybenzenesulfonamide,

2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-(trifluoromethyl)benzene sulfonamide,

N-(4-(N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)sulfamoyl)phenyl)acetamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-3,4-dimethoxybenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-2,4-dimethoxybenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methoxybenzenesulfonamide, and

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide.

6. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

2,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide,

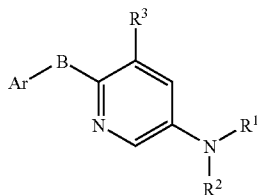
2-Chloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-fluorobenzenesulfonamide,

N-(5-Chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)-4-methylbenzenesulfonamide, and

3,4-Dichloro-N-(5-chloro-6-(isoquinolin-3-yloxy)pyridin-3-yl)benzenesulfonamide.

7. A process for the preparation of a compound of general formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1:

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wherein

Ar is an isoquinoline moiety which is substituted or unsubstituted;

B is —O—;

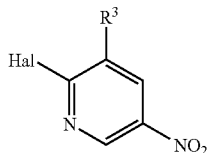
R³ is halogen, cyano, C(O)OR⁷, or C(O)NR⁸R⁹;

R⁷ is hydrogen or (C₁-C₄)alkyl;

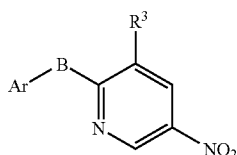
R⁸ and R⁹ are independently hydrogen or (C₁-C₆)alkyl;

R¹ is H, R² is S(O)₂R⁴, and R⁴ is substituted or unsubstituted aryl, which comprises:

a) reacting a compound of general formula (II):

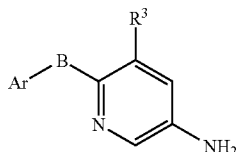


wherein Hal is fluorine, chlorine, bromine, or iodine and R³ is as defined above; with a compound of formula (III): Ar—BH wherein Ar and B are as defined above; in presence of a base such as cesium carbonate, to obtain a compound of general formula (IV);



wherein Ar, B and R³ are as defined above;

b) subjecting the nitro compound of formula (IV) above to reduction to obtain a corresponding amino compound of general formula (V);



wherein Ar, B and R³ are as defined above;

c) reacting the amino compound of general formula (V) with one equivalent of Hal-SO₂R⁴ wherein Hal is fluorine, chlorine, bromine, or iodine and R⁴ is as defined above, in the presence of a base to obtain the compound of formula (I); and,

d) optionally, converting the resulting compound into a pharmaceutically acceptable salt.

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8. A process for the preparation of a compound of general formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1:

Formula (I)

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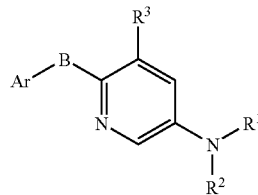
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Formula (I)



wherein

Ar is an isoquinoline moiety which is substituted or unsubstituted;

B is —O—;

R³ is halogen, cyano, C(O)OR⁷ or C(O)NR⁸R⁹;

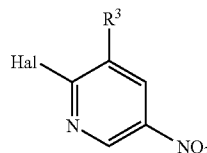
R⁷ is hydrogen or (C₁-C₄)alkyl;

R⁸ and R⁹ are independently hydrogen or (C₁-C₆)alkyl;

R¹ and R² are S(O)₂R⁴, and R⁴ is substituted or unsubstituted aryl, which comprises:

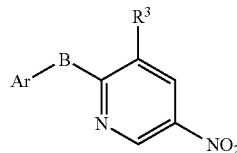
a) reacting a compound of general formula (II):

Formula (II)



wherein Hal is F, Cl, Br, or I and R³ is as defined above; with a compound of formula (III): Ar—BH wherein Ar and B are as defined above; in presence of a base such as cesium carbonate, to obtain a compound of general formula (IV);

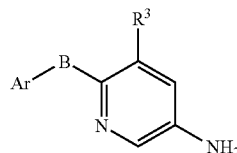
Formula (IV)



wherein Ar, B and R³ are as defined above;

b) subjecting the nitro compound of formula (IV) above to reduction to obtain a corresponding amino compound of general formula (V);

Formula (V)



wherein Ar, B and R³ are as defined above,

c) reacting the amino compound of general formula (V) with two equivalents of Hal-SO₂R⁴ wherein Hal is

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fluorine, chlorine, bromine, or iodine and R^4 is as defined above, at 45° C., in the presence of triethyl amine as a base, to obtain the compound of formula (I); and,

d) optionally, converting the resulting compound into a pharmaceutically acceptable salt.

9. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of general formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of general formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, and at least one further pharmaceutically active compound, together with a pharmaceutically acceptable carrier or diluent.

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11. A method for the treatment of a metabolic disorder related to insulin resistance or hyperglycemia, wherein the metabolic disorder related to insulin resistance or hyperglycemia is type 2 diabetes or dyslipidemia, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt thereof.

12. The method according to claim 11, wherein the metabolic disorder related to insulin resistance or hyperglycemia is type 2 diabetes.

13. The method according to claim 11, wherein the metabolic disorder related to insulin resistance or hyperglycemia is dyslipidemia.

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